BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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The Effectiveness of Immune Checkpoint Inhibitors in the Neoadjuvant and Post-Neoadjuvant Breast Cancer Settings

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H&O Could you describe the design of the KEYNOTE-522 study?

LP KEYNOTE-522 was a large, randomized, placebo-controlled phase 3 trial that tested pembrolizumab (Keytruda, Merck) as neoadjuvant and adjuvant treatment in locally advanced, nonmetastatic, triple-negative breast cancer (TNBC). A total of 1174 patients were randomly assigned in a 2:1 ratio to receive either pembrolizumab or placebo, administered in addition to 4 cycles of paclitaxel/carboplatin, every 3 weeks. This treatment was followed by 4 cycles of doxorubicin or epirubicin plus cyclophosphamide every 3 weeks, concurrent with pembrolizumab for patients in the experimental arm or placebo for patients in the control arm. All patients underwent surgery followed by adjuvant treatment that consisted of approximately 27 weeks of either pembrolizumab or placebo. The complete treatment lasted for 1 year. The primary goals of this study were to detect any differences in the rates of pathologic complete response (pCR) and event-free survival (EFS) between the 2 arms.

H&O What were the main published results of this trial?

LP After a median follow-up of 39 months, according to results that we published in the *New England Journal of Medicine* earlier this year, the estimated 36-month EFS rate was 84.5% in the pembrolizumab/chemotherapy group vs 76.8% in the placebo/chemotherapy group, for a hazard ratio for event or death of 0.63 (95% CI, 0.48-0.82; *P*<.001). Not only was EFS better with pembrolizumab than with placebo overall, but subset analyses showed improvements in all clinical and biomarker (programmed death ligand 1 [PD-L1]) subsets. Owing to variable sample sizes, the confidence intervals were broad, but the hazard ratios consistently favored pembrolizumab in all groups. Most importantly, the rate of distant recurrence was lower with pembrolizumab than with placebo, at 7.7% vs 13.1%, respectively.

Previous results of KEYNOTE-522, from the first planned efficacy analysis of 602 patients, were published in the *New England Journal of Medicine* in 2020. The analysis found a pCR of 64.8% in the pembrolizumab group and 51.2% in the placebo group (estimated treatment difference, 13.6 percentage points; 95% CI, 5.4-21.8; *P*<.001). This was a very encouraging finding because the pCR rate with pembrolizumab approached what we see in patients with human epidermal growth factor receptor 2 (HER2)–positive breast cancer treated with HER2-targeted neoadjuvant therapies. We used to consider TNBC to be a particularly poor prognosis subtype with limited treatment options, but this is no longer the case.

H&O Could you describe the updated data from KEYNOTE-522 that you recently presented?

LP I presented the final pCR rates, residual cancer burden (RCB) distribution results, and EFS rates by RCB categories in all 1174 patients accrued to the trial at the

2022 annual meeting of the American Society of Clinical Oncology. The final pCR rates were 63% in the pembrolizumab arm and 56% in the placebo arms. We also found that patients with a greater RCB after neoadjuvant chemotherapy had poorer EFS than patients with minimal residual disease or pCR. For example, an EFS event (ie, progression during neoadjuvant therapy, local or distant recurrence, second primary cancer, or death from any cause) occurred in 72.5% of pembrolizumab patients and 69.2% of placebo patients who had an RCB of 3, which represents extensive residual disease, whereas they occurred in 5.2% of pembrolizumab patients and 7.3% of placebo patients who had an RCB of 0, which is equivalent to a pCR. The addition of pembrolizumab showed a trend toward an improved hazard ratio for EFS across all clinical subsets, although with wide confidence intervals owing to variable sample sizes. The most common EFS event in both arms was distant recurrence, which was less common in the pembrolizumab arm than in the placebo arm among all RCB categories.

In the entire study population, the 3-year EFS rates were 84.5% with pembrolizumab vs 76.8% with placebo ($P<.001$). At the meeting, we presented EFS results by RCB category. Patients in the RCB0 category did well whether they received pembrolizumab or placebo, with 3-year EFS rates of 95% vs 93%, respectively. Those in the RCB1 category, which corresponds to minimal residual disease, had the same 3-year EFS rate—84%—whether they took pembrolizumab or a placebo. We saw something remarkable in the RCB2 category, which corresponds to moderate residual disease and included about 20% of the trial population. In this group, the 3-year EFS rate was 76% with pembrolizumab vs 56% with placebo—an absolute difference of 20 percentage points. This clearly shows that pembrolizumab did not work only by improving the pCR rate; it also worked by improving outcomes in patients who did not achieve a pCR. The small minority of patients in the RCB3 category did poorly in both arms, with a 3-year EFS rate of 26% with pembrolizumab and 35% with placebo. Importantly, numerically fewer patients had an outcome of RCB3 in the pembrolizumab arm compared with the control arm (5.1% vs 6.7%). What I take away from this finding is that patients who end up with extensive residual disease are in desperate need of better therapies than what we have today.

H&O In the 2020 publication of KEYNOTE-522, the effect of pembrolizumab on pCR was greater in node-positive patients than in node-negative patients. What are the possible reasons for this?

LP I do not attribute much importance to this finding, which I consider to be a statistical artifact. It is true that the addition of pembrolizumab to chemotherapy increased the pCR rate from 44% to 65% in the node-positive patients, whereas it increased pCR from 59% to 65% in the node-negative patients. This may give the impression that the addition of pembrolizumab is more effective in node-positive patients than in node-negative patients: the absolute increase in pCR was 21 percentage points vs just 6 percentage points. What I am seeing, however, is that in node-negative patients, a change in nodal status cannot contribute to differences in the pCR rate because the higher pCR rate in both arms is caused by these patients starting out with negative nodes. The confidence intervals for the pCR odds ratios in the 2 nodal groups also broadly overlap, indicating that the observed difference is not statistically significant.

More importantly, the updated article that we published earlier this year reports that node-negative patients benefitted just as much—or even more—as node-positive patients when it came to improvement in EFS rates (hazard ratio, 0.58 in node-negative patients and 0.65 in node-positive patients). I believe that there is no strong or consistent signal that pembrolizumab has a differential efficacy based on the nodal status.

H&O We saw that patients in KEYNOTE-522 who experienced a pCR had excellent outcomes, regardless of treatment. Does this finding affect the use of post-neoadjuvant pembrolizumab in patients who experience a pCR with a KEYNOTE-522–type regimen?

LP This question is very important because patients who experience a pCR with chemotherapy alone do very well, as earlier studies have established. As expected, patients in the chemotherapy-alone group in KEYNOTE-522 did well if they experienced a pCR, although patients who also received pembrolizumab did even a little bit better if they experienced a pCR. The 3-year EFS was 95% among patients who experienced a pCR with pembrolizumab vs 93% among those who experienced a pCR with placebo, although this difference was not statistically significant.

My recommendation is to use therapies as they were used in the pivotal studies, recognizing that every study that answers a question also raises new ones. One important practical point is that for patients with residual disease, particularly RCB2 and RCB3 disease, I also recommend adding capecitabine to pembrolizumab treatment for 6 to 8 cycles. Unfortunately, the US Food and Drug Administration did not allow modification to the KEYNOTE-522 design to include adjuvant capecitabine, and therefore no patients in this study received concurrent capecitabine and pembrolizumab. However, the safety of this combination was shown in a small phase 2

trial in metastatic cancer, and the benefit from adjuvant capecitabine in patients with residual cancer after neoadjuvant chemotherapy was established by the CREATE-X trial. The CREATE-X results are likely applicable to the KEYNOTE-522 population as well. Adjuvant olaparib (Lynparza, AstraZeneca) is an even better alternative to adjuvant capecitabine in patients who are germline BRCA-positive. My threshold for stopping maintenance (ie, adjuvant) pembrolizumab—for side effects, logistical issues, or cost—is lowest for patients in the RCB0 or RCB1 categories. I would push for continuing pembrolizumab, if safely possible, in patients with RCB2 disease. Patients in the RCB3 category do badly whether they receive pembrolizumab or not, so they need better therapies, and they definitely need capecitabine.

H&O How much of a role did post-neoadjuvant therapy play in KEYNOTE-522?

LP From KEYNOTE-522, we know that patients who achieved less than a pCR benefitted from pembrolizumab, but we cannot tell from the study design how much the maintenance phase contributed to outcomes. We will have some data in the future because the Breast Cancer Steering Committee of the National Cancer Institute has approved a large, prospective clinical trial that will randomly assign patients who have experienced a pCR with the KEYNOTE-522 regimen to continue with adjuvant pembrolizumab or receive no further pembrolizumab. We expect this study to be launched later this year or in early 2023 by the ECOG-ACRIN Cancer Research Group. The still-ongoing S1418 adjuvant pembrolizumab trial will also provide important information.

H&O How does KEYNOTE-522 affect the way we evaluate pCR as a short-term endpoint?

LP Our findings confirm the validity of pCR as a surrogate endpoint, given that the improvement in the pCR rate translated into an improvement in the EFS rate. In fact, both the pCR and EFS rates improved by a similar amount of approximately 7 percentage points. However, it is increasingly clear that differences in pCR rates do not completely predict subsequent improvements in EFS rates. Some agents lead to double-digit improvements in pCR rates, but only small or even nonexistent improvements in EFS rates. We hypothesize that the overall shift to smaller residual disease burden over the entire residual disease spectrum, as seen in KEYNOTE-522, predicts improvement in EFS rates better than differences in pCR rates alone. Agents that move patients from RCB1 to RCB0 categories but have little impact on RCB2 and RCB3 distributions would increase the pCR rate but would have very little effect on EFS rates because patients in both the RCB0 and RCB1 categories have a relatively good outcome. We recently published an article, with Marczyk as the first author, that describes the statistical model and free web tool we built to capture the RCB shift between trial arms.

H&O Could you describe your work using durvalumab and olaparib in neoadjuvant and post-neoadjuvant therapy in hormone receptor (HR)–positive breast cancers?

LP I led the durvalumab (Imfinzi, AstraZeneca) arm of the I-SPY2 trial. The rationale behind adding durvalumab to weekly paclitaxel neoadjuvant chemotherapy was similar to that of the KEYNOTE-522 trial, although I-SPY2 differed in that it included patients with both HR-positive and HR-negative disease (in both KEYNOTE-522 and I-SPY2, patients included in the immunotherapy arms were HER2-negative). The use of immunotherapy in breast cancer began in patients with TNBC because these cancers have large numbers of tumor-infiltrating lymphocytes. A subset of HR-positive breast cancers, however—6% to 20%, depending on the definition—also have a high level of immune presence in the microenvironment that is very similar to that seen in TNBC. Because HR-positive breast cancer is so much more common than TNBC, the actual number of HR-positive, immune-rich cancers may be higher in HR-positive BC than in TNBC. In I-SPY2, we wanted to test if the addition of an immune checkpoint inhibitor to neoadjuvant chemotherapy would benefit HR-positive patients as well as patients with TNBC. We found that the addition of durvalumab and olaparib improved the pCR rate in HR-positive patients as well as in TNBC, but the effect among HR-positive patients was dramatically different by MammaPrint status. HR-positive patients with MammaPrint–ultra-high status experienced a near-tripling of the pCR rate from 22% in the control group to 64% in the durvalumab group. By contrast, HR-positive patients with MammaPrint-high status had low pCR rates of 10% in both arms. This observation is important because it supports the use of an existing standard-of-care test, MammaPrint, to determine which HR-positive patients might benefit from the addition of an immunotherapy agent to therapy. The HR-positive MammaPrint–ultra-high cancers are also characterized by low expression of HR-related genes, and therefore are less likely to benefit from adjuvant endocrine therapy despite being HR-positive. I should add that in I-SPY2, the durvalumab arm also included concurrent administration of olaparib. We believe that the improvement in the pCR rate was from

the durvalumab rather than from the olaparib, however, based on information derived from several other trials that tested various combinations of chemotherapy plus olaparib (and other poly[ADP-ribose polymerase] inhibitors) and durvalumab. I am also very pleased to announce that we are planning a large, randomized trial (S2206) through the SWOG Cancer Research Network that will test the I-SPY2 results and will recruit patients with HR-positive MammaPrint–ultra-high cancers and randomize them to standard-of-care neoadjuvant chemotherapy alone vs standard-of-care neoadjuvant chemotherapy plus durvalumab.

H&O What would you say is the next step in research?

LP First, we need to devise a better way to treat patients with extensive residual cancer—that is, the RCB3 group—who still fare very badly. We also want to improve the results in patients with RCB2 disease and reduce the 14% recurrence rate. Antibody-drug conjugates are the most promising agents to explore in this space. Combining pembrolizumab with other immunotherapy agents is also worth exploring.

Second, we need to be able to identify which patients are most likely to develop immune-related adverse events. The inconvenient truth is that as many as 20% of patients who receive an immune checkpoint inhibitor experience immune-related adverse events that are clinically significant. The most common is thyroid hormone abnormalities. Fortunately, this adverse event is easy to manage with a daily hormone supplement, but of course this adds to treatment cost and means that we have caused a new disease for the patient. Other immune-related adverse events can also occur, such as colitis, hepatitis, diabetes, and lethal cases of Guillain-Barré syndrome. The ability to identify those patients at risk for immune-related adverse events, and potentially prevent these adverse events from occurring, is a highly challenging and important area of research.

Third, it would be helpful if we could predict which patients would benefit from immunotherapy, which is expensive and potentially toxic. In metastatic TNBC, we have PD-L1 expression to identify patients who could benefit from pembrolizumab plus chemotherapy, but we have no such marker in early-stage TNBC. In all neoadjuvant immunotherapy trials, both PD-L1–positive and PD-L1–negative cancers demonstrated improved pCR rates with immunotherapy.

H&O When do you plan to present results of the S1418 study from SWOG, and what do you expect the effect to be?

LP S1418 is a phase 3 trial that is looking at the addition of pembrolizumab to standard-of-care adjuvant treatment in patients with TNBC who have residual disease after chemotherapy (NCT02954874). In S1418, no patient received neoadjuvant immunotherapy. A member of the study's interim data safety monitoring committee has told me that we do not have enough events to declare success or failure at this point, but we anticipate that sufficient events will accrue by the end of 2023 to assess efficacy.

If the study is positive, I think the effect will be to make people feel more comfortable with the idea of using adjuvant pembrolizumab. It will also provide an alternative strategy to improve outcome for those who for some reason cannot or otherwise would not receive neoadjuvant pembrolizumab. If the results are negative, it will make people much more comfortable with discontinuation of treatment for certain patients, such as those in the RCB0 and RCB1 groups.

Disclosure

Dr Pusztai has received consulting fees and honoraria for advisory board participation from Pfizer, AstraZeneca, Merck, Novartis, Bristol Myers Squibb, GlaxoSmithKline, Genentech, Personalis, Daiichi Sankyo, Natera, and Exact Sciences, and has received institutional research funding from Seagen, GlaxoSmithKline, AstraZeneca, Merck, Pfizer, and Bristol Myers Squibb.

Suggested Readings

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